No. 99

SYNTHESES IN THE EPINEPHRINE SERIES

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(From the Transactions of the Chemical Society, Vol. 95, 1909)

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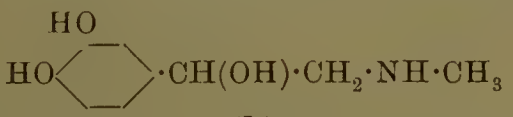
CCXXVII.—*Syntheses in the Epinephrine Series.*

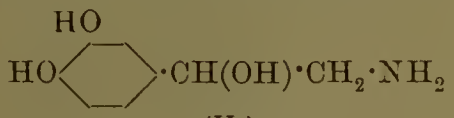
By Frank Tutin, Frederic William Caton, and Archie Cecil Osborn Hann.

Inasmuch as the base epinephrine, which possesses a constitution represented by formula I (Jowett, Trans., 1904, **85**, 192), has so valuable a physiological action, it appeared to be of considerable interest to prepare certain substances related to it, in order that their properties might be physiologically investigated:

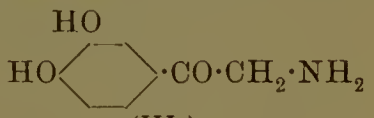


(I.)

It is already known that the ketone corresponding with epinephrine is physiologically active, as are also the primary amines (II and III) corresponding with both these compounds:

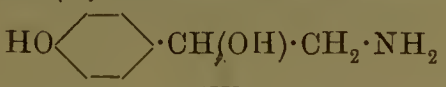


(II.)

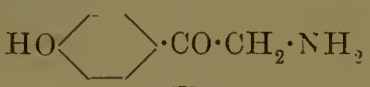


(III.)

We therefore endeavoured to prepare bases analogous to the above-mentioned primary amines, but which would contain only one hydroxyl group in the benzene nucleus. This attempt has been successful, in so far as the para-derivatives are concerned, for *β*-p-*dihydroxy-β-phenylethylamine* (IV) and the corresponding *ketone* (V) have been obtained:



(IV.)

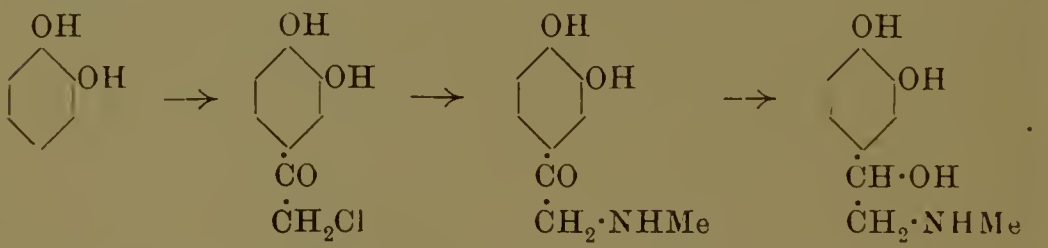


(V.)

The physiological action of these substances has been investigated by Dr. H. H. Dale, Director of the Wellcome Physiological Research Laboratories, to whom we now express our thanks. It has thus been ascertained that both the bases (IV and V), when injected intravenously, have a pronounced influence on the blood-pressure. The intensity of the action of the keto-base is of the same order as that of the ketone corresponding with epinephrine, and it causes about one-tenth of the rise in blood-pressure produced by an equal weight of *β-p*-hydroxyphenylethylamine, $HO\cdot C_6H_4\cdot CH_2\cdot CH_2\cdot NH_2$ (Barger, this vol., p. 1123). The reduction of the ketonic group in the monohydroxy-base (V) is, however, not attended with that enormous increase in activity which is observed when the ketone corresponding with epinephrine is reduced, as *β-p*-dihydroxy-

β-phenylethylamine (IV) possesses only about twice the activity of its corresponding ketone. The action of the reduced base is, however, qualitatively far more like that of epinephrine than is that of the ketonic compound.

The first synthesis of epinephrine to be described was conducted according to the following scheme (D.R.-P. 152814, 155632, and 157300):



We therefore endeavoured, in the first place, to prepare β-*p*-dihydroxy-β-phenylethylamine (IV) by a similar series of reactions, but with the employment of phenol, instead of catechol, as the initial material.

Kunckell and Johannssen (*Ber.*, 1898, **31**, 169) prepared ω-chloro-*p*-hydroxyacetophenone by the action of chloroacetyl chloride on anisole in the presence of an excess of aluminium chloride, but they failed to obtain the desired compound directly from phenol. The present authors, however, find that the chloroketone can be formed from phenol by means of the Friedel-Crafts reaction if nitrobenzene be employed as the solvent. The yield obtained by this method is, however, but small. The above-mentioned authors (*loc. cit.*) have shown that ω-chloro-*p*-hydroxyacetophenone chloroacetate is formed by the action of aluminium chloride and chloroacetyl chloride on phenyl chloroacetate. The present authors therefore sought to obtain the corresponding acetate in an analogous manner from phenyl acetate, as the former compound would serve equally as well as the hydroxy-ketone, from which it is derived, for the preparation of the desired amine, and the use of the relatively costly anisole would thus be avoided. It was found, however, that when a mixture of phenyl acetate and chloroacetyl chloride is treated with aluminium chloride, the acetyl group wanders into the para-position, and its place is taken by the chloroacetyl radicle, the resulting compound being p-*hydroxyacetophenone chloroacetate* (m. p. 73—74°). We therefore prepared ω-chloro-*p*-hydroxyacetophenone according to the method of Kunckell and Johannssen.

It was found impossible to obtain ω-amino-*p*-hydroxyacetophenone from the chloro-ketone by condensation with ammonia, although the experiment was conducted under a great variety of conditions. Attempts to prepare the corresponding methyl

derivative from methylamine were also unsuccessful. This result was somewhat surprising, as the corresponding dihydroxyphenylmethylamino-ketone is formed in an analogous manner without much difficulty (D.R.-P. 155632). The only definite product that could be obtained by the action of ammonia on ω-chloro-*p*-hydroxyacetophenone was an *additive* compound, $HO{\cdot}C_6H_4{\cdot}CO{\cdot}CH_2Cl,NH_3$.

The desired base, *ω-amino*-p-*hydroxyacetophenone* (m. p. 190—193°), was, however, eventually obtained in the following manner. *ω-Chloro*-p-*acetoxyacetophenone* (m. p. 89—90°) was heated with potassium phthalimide, when the *phthalyl* derivative,

$$OAc{\cdot}C_6H_4{\cdot}CO{\cdot}CH_2{\cdot}N\begin{matrix}CO\\CO\end{matrix}C_6H_4$$

(m. p. 174°), was obtained. This condensation product was then heated with concentrated hydrochloric acid, when *ω-amino*-p-*hydroxyacetophenone hydrochloride* was generated. The free base obtained from this salt crystallises well, and is quite stable in the absence of oxygen, a behaviour which is not at all in agreement with the statement of Gabriel (*Ber.*, 1908, **41**, 1128) that α-aminoketones of this type cannot exist in the free state.

The next step was to reduce the ketonic group contained in the above-described base, in order to obtain the final product. It was found, however, that this could not be accomplished in a manner analogous to that by which epinephrine was obtained from its corresponding ketone, namely, by the action of aluminium amalgam. The behaviour of other reducing agents was therefore investigated, when it was found that the desired result was attained by the use of sodium and alcohol. The β-*p*-dihydroxy-β-phenylethylamine (IV) so obtained darkened and absorbed oxygen rapidly on exposure to the air, and could not be crystallised, and this was also the case with its hydrochloride. It readily yielded, however, a crystalline *tribenzoyl* derivative (m. p. 182°), by means of which the identity of the substance was verified.

At the stage in this work when it was found that the desired ketonic base could not be obtained by the action of ammonia on the corresponding chloro-compound, it was thought that the object might be attained by the method first employed by Jowett (Trans., 1905, **87**, 967) for syntheses in the epinephrine series, which has since been used with some success by others (Böttcher, *Ber.*, 1909, **42**, 253; Pauly and Neukam, *Ber.*, 1908, **41**, 4151; Mannich and Jacobson, *Chem. Zeitsch.*, 1909, **33**, 923). For this purpose we endeavoured to prepare α-hydroxy-*p*-methoxy-α-phenylethane, in order that, by the elimination of water from this compound, *p*-vinylphenol might be obtained. *p*-Hydroxyacetophenone was therefore reduced, but this only resulted in the formation of a

pinacone (m. p. 207—208°). We then prepared *α-p-hydroxyphenylethylamine* by the reduction of *p*-hydroxyacetophenoneoxime. The base was subsequently heated with nitrous acid, but the resulting product, which presumably contained *α-p*-dihydroxy-*α*-phenylethane, was very unstable when exposed to the air, rapidly yielding acetaldehyde and a brown resin.

α-p-Hydroxyphenylethylamine possesses special interest, inasmuch as it was found to have a physiological action similar to that exerted by its *β*-isomeride, which has been shown by Barger (*loc. cit.*) to be one of the active principles of ergot. The naturally occurring compound is, however, very considerably more active. An attempt was furthermore made to prepare *p*-vinylphenol by the dry distillation of *p*-coumaric acid, under the same conditions as lead to the formation of the corresponding ortho-compound (*Ber.*, 1908, **41**, 367), but only polymerised products could be obtained.

As we were unsuccessful in preparing *p*-vinylphenol, *p*-vinylanisole (Klages, *Ber.*, 1903, **36**, 3590) was employed. From the latter, the *dibromide* (m. p. 80—81°) was obtained, and this, by means of aqueous acetone, was converted into the *bromohydrin*, $MeO{\cdot}C_6H_4{\cdot}CH(OH){\cdot}CH_2Br$, which is a liquid. No satisfactory method, however, could be devised of converting the latter compound into the corresponding amine, the yields of basic product being extremely small. It is interesting to note that on treatment with acetyl chloride, the hydroxyl group in the bromohydrin is replaced by chlorine, the resulting *α-chloro-β-bromo*-p-*methoxy-α-phenylethane*, $MeO{\cdot}C_6H_4{\cdot}CHCl{\cdot}CH_2Br$, being a solid, melting at 39—40°. It has been stated by Muset (*Bull. Acad. roy. Belg.*, 1906, 775) that the replacement of hydroxyl by chlorine through the agency of acetyl chloride is characteristic of tertiary alcohols, but the above change shows that this is not always the case.

Some experiments were also made with the object of obtaining ortho- and meta-compounds corresponding with the above-described *β-p*-dihydroxy-*β*-phenylethylamine. *o*-Vinylphenol was prepared by the dry distillation of *o*-coumaric acid, but no dibromide could be obtained from it. *m*-Vinylphenol was prepared from *m*-nitrocinnamic acid, according to the method of Komppa (*Ber. Ref.*, 1893, **26**, 677), but the yield of the final product was so small that we did not proceed further in this direction. The derivatives of *m*-aminostyrene thus obtained did not, however, agree in their properties with the corresponding substances described by Komppa (*loc. cit.*). The last-mentioned author appears to have regarded the hydrochloride and benzoyl derivative as being anhydrous, and stated that the latter substance fused at 90—91°. These compounds, as prepared by the present authors, do not crystallise

except with one molecule of water, and melt respectively at 181° and 126—127°.

Experimental.

ω-*Chloro*-p-*hydroxyacetophenone.*

Kunckell and Johannssen (*Ber.*, 1898, **31**, 167) prepared ω-chloro-*p*-hydroxyacetophenone by the action of chloroacetyl chloride and excess of aluminium chloride on anisole, but, when they attempted to obtain it directly from phenol, the experiment resulted in the formation of phenyl chloroacetate, and subsequently of ω-chloro-*p*-hydroxyacetophenone chloroacetate. With the object of obtaining from phenol the acetate corresponding with the last-mentioned compound, the present authors treated phenyl acetate with chloroacetyl chloride and aluminium chloride.

Thirteen grams of phenyl acetate and an equal weight of chloroacetyl chloride were dissolved in carbon disulphide, and treated with 17 grams of powdered aluminium chloride. After heating the mixture for six hours, the solvent was removed, and ice and dilute hydrochloric acid were added. The product was then extracted with ether, when, on removing the solvent, a light green oil was obtained, which became partly solid when stirred with light petroleum. The solid was drained on a tile, after which it was recrystallised from benzene, when colourless needles, melting at 73—74°, were obtained:

0·1869 gave 0·3850 CO_2 and 0·0729 H_2O. C = 56·2; H = 4·3.

$C_{10}H_9O_3Cl$ requires C = 56·5; H = 4·2 per cent.

That this compound was p-*hydroxyacetophenone chloroacetate* was evident from the fact that, on treatment with ammonia, it yielded *p*-hydroxyacetophenone and the base,

$$NH_2{\cdot}CO{\cdot}CH_2{\cdot}NH{\cdot}CH_2{\cdot}CO{\cdot}NH_2,$$

which was obtained by Heintz bv the action of ammonia on ethyl chloroacetate (*Annalen*, 1868, **148**, 177). It is evident, therefore, that the acetyl group had wandered into the para-position, its place being taken by the chloroacetyl radicle.

In view of the statements of Behn (D.R.-P. 95901), we attempted to obtain ω-chloro-*p*-hydroxyacetophenone directly from phenol by means of aluminium chloride, but with the use of nitrobenzene as a solvent. Although this operation was successful, the yield was so small that we returned to the original method of Kunckell and Johannssen (*loc. cit.*), using, however, an improved means of isolating the product.

Twenty grams of anisole and 24 grams of chloroacetyl chloride were dissolved in carbon disulphide, and 60 grams of aluminium chloride gradually introduced. After heating for about four hours,

the solvent was removed, the residue treated with ice and hydrochloric acid, and the product extracted with ether. The ethereal liquid thus obtained was shaken with a solution of ammonium carbonate, which removed a small amount of brown product, after which it was treated with aqueous sodium carbonate. This removed the ω-chloro-*p*-hydroxyacetophenone in a state of relative purity. During these operations a most severe irritation of the eyes and face was experienced. This was found to be due to the formation of a small amount of *ω-chloro-o-methoxyacetophenone*, a substance which will be described in a subsequent communication. The sodium carbonate extracts were acidified, and the precipitated product crystallised from methyl alcohol, when ω-chloro-*p*-hydroxyacetophenone was obtained in the form of light yellow laminæ, melting at 148°.

Action of Ammonia and Methylamine on ω-Chloro-p-hydroxyacetophenone.

A quantity of ω-chloro-*p*-hydroxyacetophenone was dissolved in alcohol, and a solution of ammonia in absolute alcohol added. The mixture became red, some heat being developed, and a crystalline substance soon separated. The latter was collected, and recrystallised from an alcoholic solution of ammonia. It was then found to be an *additive* compound of the chloro-ketone and one molecule of ammonia, the latter being held only rather loosely:

0·3010, dissolved in alcohol, neutralised 16·0 c.c. $N/10$-H_2SO_4. $NH_3 = 9·0$.

$C_8H_7O_2Cl,NH_3$ requires $NH_3 = 9·1$ per cent.

On keeping this substance for any considerable length of time in contact with aqueous or alcoholic ammonia, or on heating it with either of these reagents, only red, tarry products resulted. This was also the case when only the theoretical amount of ammonia was employed. Analogous experiments, conducted with the use of methylamine, likewise resulted only in the formation of red, amorphous products.

Condensation of ω-Chloro-p-acetoxyacetophenone with Potassium Phthalimide.

Since it was found impossible to obtain an amine from the chloro-ketone by condensation with ammonia, recourse was had to the use of potassium phthalimide. It was found necessary, however, to employ the acetyl derivative of the chloro-ketone, since the original substance was so acidic that it decomposed the potassium phthalimide.

ω-Chloro-*p*-hydroxyacetophenone was boiled for one hour with acetic anhydride, and the resulting acetylated product purified by distillation. *ω-Chloro*-p-*acetoxyacetophenone* crystallises from alcohol in large prisms, which melt at 89—90°:

0·1553 gave 0·3218 CO_2 and 0·0592 H_2O. C = 56·5; H = 4·2.

$C_{10}H_9O_3Cl$ requires C = 56·5; H = 4·2 per cent.

After numerous experiments, the following method of condensing the acetyl derivative of the chloro-ketone with potassium phthalimide was found to be the best, a yield of phthalide derivative amounting to about 42 per cent. of that theoretically possible being obtained. ω-Chloro-*p*-acetoxyacetophenone was heated in a nickel crucible to 120—125°, when a molecular proportion of finely-powdered potassium phthalimide was gradually introduced, with constant stirring. The mixture, which was at first quite fluid, gradually became viscid, and, after being maintained at the above temperature for about half an hour, was completely converted into a brown solid. The latter, after being powdered, was extracted in a Soxhlet apparatus with boiling benzene. On concentrating the benzene extract, the condensation product, together with phthalimide, separated in crystals. The solid was collected, washed with benzene, and freed from phthalimide by repeated extraction with boiling water, after which the phthalide derivative was crystallised from alcohol. It then formed slender, colourless needles, melting at 174°:

0·1476 gave 0·3627 CO_2 and 0·0574 H_2O. C = 67·0; H = 4·3.

0·3785 „ 14·8 c.c. N_2 (moist) at 20·8° and 766 mm. N = 4·5.

$C_{18}H_{13}O_5N$ requires C = 66·9; H = 4·0; N = 4·3 per cent.

p-Acetoxy-ω-phthaliminoacetophenone,

$$AcO\cdot C_6H_4\cdot CO\cdot CH_2\cdot N\!<\!\begin{matrix}CO\\CO\end{matrix}\!>\!C_6H_4,$$

is rather sparingly soluble in alcohol, but more readily soluble in benzene, ethyl acetate, or glacial acetic acid. It is insoluble in water or light petroleum.

ω-Amino-p-*hydroxyacetophenone.*

The above-described phthalide derivative (2 parts), together with glacial acetic acid (15 parts) and concentrated hydrochloric acid (50 parts), was heated in sealed tubes to 130° for three hours. The contents of the tubes, which had become brown, were united, concentrated under diminished pressure, and freed from phthalic acid by extraction with ether. The liquid was then treated with animal charcoal, filtered, and evaporated to dryness under diminished pressure, as it is necessary to avoid the access of air

so far as possible. The dry residue was dissolved in alcohol, and after some time *ω-amino*-p-*hydroxyacetophenone hydrochloride* separated in pink prisms, which were obtained colourless by further recrystallisation from alcohol. This hydrochloride dissolves very readily in water, but only moderately so in alcohol, and not at all in ethyl acetate. It has no definite melting point, but decomposes at 245—252°:

0·2644 gave 0·1982 AgCl. Cl = 18·6.

$C_8H_9O_2N$,HCl requires Cl = 18·9 per cent.

ω-Amino-p-*hydroxyacetophenone* was obtained from the aqueous solution of its hydrochloride by precipitation with sodium carbonate. It forms colourless plates, which melt and decompose at 190—193°:

0·0982 gave 0·2278 CO_2 and 0·0546 H_2O. C = 63·4; H = 6·2.

0·1137 „ 0·2660 CO_2 „ 0·0644 H_2O. C = 63·8; H = 6·3.

$C_8H_9O_2N$ requires C = 63·6; H = 6·0 per cent.

It is only with difficulty that this base can be obtained colourless, as in contact with air and moisture, especially in alkaline solutions, it rapidly acquires a brilliant pink colour. It is readily soluble in both acids and alkali hydroxides, very sparingly so in water, alcohol, or ethyl acetate, and insoluble in chloroform or ether. It yields a *picrate*, which crystallises in needles, melting at 192°, but its gold and platinum salts were too soluble to admit of their isolation.

ω-Benzoylamino-p-*benzoyloxyacetophenone*,

$$BzO\cdot C_6H_4\cdot CO\cdot CH_2\cdot NHBz,$$

was prepared by the Schotten-Baumann method. It forms colourless needles, melting at 173—174°:

0·0992 gave 0·2685 CO_2 and 0·0439 H_2O. C = 73·8; H = 4·9.

$C_{22}H_{17}O_4N$ requires C = 73·6; H = 4·7 per cent.

β-p-*Dihydroxy-β-phenylethylamine.*

Attempts were first made to reduce ω-amino-*p*-hydroxyacetophenone by means of aluminium amalgam, in a manner similar to that by which epinephrine has been obtained from its corresponding ketone (D.R.-P. 157300), but, although some change was effected by this means, the desired result was not attained. It was found, however, that sodium and boiling alcohol is a satisfactory reducing agent for this purpose.

Five grams of ω-amino-*p*-hydroxyacetophenone hydrochloride were dissolved in 250 c.c. of absolute alcohol in a flask attached to a reflux condenser, and 30 grams of metallic sodium gradually introduced in small pieces, under such conditions that the liquid was kept in a state of rapid ebullition. When the metal had

dissolved, the mixture was quickly cooled, after which concentrated hydrochloric acid was added until the liquid ceased to be alkaline to litmus. The precipitated sodium chloride was then removed, the filtrate evaporated to dryness under diminished pressure, and the residue extracted with absolute alcohol. In this way, the remaining small amount of sodium chloride was removed. The alcoholic extracts were concentrated, ethyl acetate added, and the resulting mixture again evaporated. A relatively small amount of the unchanged hydrochloride then separated in a crystalline condition, and was removed. The filtrate contained a *hydrochloride*, which was nearly insoluble in ethyl acetate, but could not be induced to crystallise. When dissolved in water, this salt absorbed oxygen, even at the ordinary temperature, and this change occurred rapidly on evaporating the aqueous solution with the aid of heat. On rendering the solution of the salt alkaline with sodium carbonate, a base was precipitated, but this substance, like its hydrochloride, could not be crystallised, and it rapidly absorbed oxygen. The identity of this base as *β*-p-*dihydroxy-β-phenylethylamine* was, however, proved by means of its benzoyl derivatives.

A quantity of the aqueous solution of the reduced hydrochloride was benzoylated by means of the Schotten-Baumann reaction. The product so obtained was crystallised from alcohol, when it melted at 145—175°, and obviously consisted of a mixture. By crystallisation from benzene, it was ultimately separated into two substances, the more readily soluble of which formed slender needles, melting at 182°:

0·0999 gave 0·2737 CO_2 and 0·0461 H_2O. C = 74·7; H = 5·1.
$C_{29}H_{23}O_5N$ requires C = 74·8; H = 4·9 per cent.

0·3110 in 30·6 of nitrobenzene gave Δt − 0·170°. M.W. = 419.
0·3572 „ 35·0 „ „ „ Δt − 0·170°. M.W. = 420.
$C_{29}H_{23}O_5N$ requires M.W. = 465.

It is evident from the above results that this substance was the *tribenzoyl* derivative of *β*-p-*dihydroxy-β-phenylethylamine*, $BzO{\cdot}C_6H_4{\cdot}CH(OBz){\cdot}CH_2{\cdot}NHBz$, the molecular weight determinations clearly showing that it could not be a derivative of a pinacone.

The more sparingly soluble constituent of the above-described mixture melted at 210°, and, when pure, formed glistening leaflets, which were nearly insoluble in benzene. It proved to be a *dibenzoyl* derivative corresponding with the above-mentioned tribenzoyl compound, since it readily yielded the latter on further treatment with benzoyl chloride. Moreover, since the tribenzoyl derivative, when boiled with 80 per cent. alcohol, yielded this

dibenzoyl compound, melting at 210°, it would appear that the latter possesses the structure $BzO\cdot C_6H_4\cdot CH(OH)\cdot CH_2\cdot NHBz$:

0·1017 gave 0·2736 CO_2 and 0·0486 H_2O. C = 73·4; H = 5·3.
0·1070 „ 0·2860 CO_2 „ 0·0500 H_2O. C = 72·9; H = 5·2.
$C_{22}H_{19}O_4N$ requires C = 73·1; H = 5·3 per cent.

The results of the physiological experiments, recorded in the introductory portion of this paper, also afford confirmation of the fact that *β*-*p*-dihydroxy-*β*-phenylethylamine had been formed by the reduction of the *ω*-amino-*p*-hydroxyacetophenone, although the former compound could not be isolated in a state of purity.

As previously stated, attempts were made to prepare some of the above-described compounds by other means. Although the desired results were not thus attained, these experiments led to the production of a variety of new compounds, which are described below.

p-Hydroxyacetophenone was reduced by means of sodium amalgam, both in alkaline and acid solutions, and also by aluminium amalgam. The greater part of the product was, in each case, a viscid oil, but a crystalline solid was also formed, the amount of the latter being greatest when the neutral reducing agent was employed.

Twenty grams of *p*-hydroxyacetophenone were dissolved in a large volume of aqueous methyl alcohol, and a quantity of aluminium amalgam added. The mixture was kept, with occasional stirring, until the aluminium had disappeared, when the product was extracted with ether. The material obtained after removing the solvent was dissolved in ethyl acetate, when 7·5 grams of a solid, in the form of a crystalline powder, gradually separated. This product was crystallised from alcohol, when it formed small, colourless prisms, which melted at 207—208°. It was sparingly soluble in alcohol and in water, and nearly insoluble in ethyl acetate:

0·1523 gave 0·3908 CO_2 and 0·0914 H_2O. C = 69·6; H = 6·7.
$C_8H_{10}O_2$ requires C = 69·6; H = 7·2 per cent.
$C_{16}H_{18}O_4$ „ C = 70·1; H = 6·6 „

This substance proved to be the *pinacone*, $C_{16}H_{18}O_4$, and not the desired secondary alcohol, as shown by the molecular weight of its *tetra-acetyl* derivative. The latter compound, formed in the usual way, crystallised from alcohol in colourless leaflets, which melted at 188—189°:

0·1293 gave 0·3086 CO_2 and 0·0710 H_2O. C = 65·1; H = 6·1.
$C_{24}H_{26}O_8$ requires C = 65·2; H = 5·9 per cent.

0·1760 in 19·5 of benzene gave $\Delta t - 0·125°$. M.W. = 410.
0·1098 „ 22·2 „ naphthalene gave $\Delta t - 0·080°$. M.W. = 426.
$C_{24}H_{26}O_8$ requires M.W. = 442.

α-p-*Hydroxyphenylethylamine.*

Eight grams of *p*-hydroxyacetophenoneoxime (m. p. 144—145°) were dissolved in 100 c.c. of aqueous methyl alcohol, and twice the theoretical amount of 2 per cent. sodium amalgam gradually introduced in small pieces, the mixture being constantly maintained acid by the frequent addition of acetic acid. When all reaction had ceased, the liquid was extracted with ether to remove unchanged oxime, after which it was rendered alkaline by means of potassium carbonate, and repeatedly extracted with amyl alcohol. The resulting amyl-alcoholic liquids were extracted with successive quantities of dilute hydrochloric acid, and the combined acid liquids concentrated under diminished pressure. *α*-p-*Hydroxyphenylethylamine hydrochloride* then separated in stout prisms, which were purified by recrystallisation from water. This salt is soluble in alcohol, and insoluble in ethyl acetate; it possesses no definite melting point, but gradually softens, and darkens at 200—280°. Above the latter temperature it yields a sublimate of ammonium chloride, together with phenol, but it was ascertained that no *p*-vinylphenol was formed:

0·1527 gave 0·3086 CO_2 and 0·0964 H_2O. C = 55·1; H = 7·0.
$C_8H_{12}ONCl$ requires C = 55·4; H = 6·9 per cent.

α-p-*Hydroxyphenylethylamine*, as obtained from its hydrochloride, was sparingly soluble in water or alcohol, and insoluble in ether or chloroform. It formed an amorphous, gum-like mass, which could not be crystallised.

The *dibenzoyl* derivative, prepared by the Schotten-Baumann method, crystallises from dilute alcohol in fine needles, and melts at 187—188°:

0·1528 gave 0·4280 CO_2 and 0·0758 H_2O. C = 76·4; H = 5·5.
$C_{22}H_{19}O_3N$ requires C = 76·5; H = 5·5 per cent.

α-p-*Hydroxy*-N-*benzoylphenylethylamine*, $HO{\cdot}C_6H_4{\cdot}CHMe{\cdot}NHBz$, was formed on heating the dibenzoyl derivative with 5 per cent. alcoholic potash. It crystallises from alcohol in large, hexagonal prisms, melting at 156°:

0·1125 gave 0·3096 CO_2 and 0·0631 H_2O. C = 75·0; H = 6·2.
$C_{15}H_{15}O_2N$ requires C = 74·8; H = 6·2 per cent.

Several attempts were made to prepare *α*-*p*-dihydroxy-*α*-phenylethane by the action of heat on the nitrite of *α*-*p*-hydroxyphenylethylamine, but the products so obtained were very unstable in the

presence of air, rapidly yielding acetaldehyde and a brown resin. An experiment was therefore conducted in an atmosphere of carbon dioxide, and the product immediately acetylated by means of acetic anhydride. An oil was thus obtained, which distilled at about 200°/20 mm., and, on analysis, yielded the following result:

0·1522 gave 0·3723 CO_2 and 0·0916 H_2O. C = 66·7; H = 6·7.

$C_{10}H_{12}O_3$ requires C = 66·7; H = 6·6 per cent.

It would thus appear that this liquid was a *monoacetyl* derivative of α-p-*dihydroxy*-α-*phenylethane*.

p-*Vinylanisole Derivatives*.

α-Hydroxy-*p*-methoxy-α-phenylethane was prepared from anisaldehyde by means of the Grignard reaction, and, with the use of hydrochloric acid, was converted into the chloride. The latter, on treatment with pyridine, forms *p*-vinylanisole (Klages, *Ber.*, 1903, **36**, 3595).

αβ-Dibromo-p-*methoxy*-α-*phenylethane*, $MeO{\cdot}C_6H_4{\cdot}CHBr{\cdot}CH_2Br$, was formed by the gradual addition of a cold ethereal solution of bromine to a solution of *p*-vinylanisole in the same solvent, cooled in ice. The new compound, which separates from the ether, was purified by recrystallisation from light petroleum, when it formed long, prismatic needles, melting at 80—81°:

0·1351 gave 0·1710 AgBr. Br = 53·9.

$C_9H_{10}OBr_2$ requires Br = 54·4 per cent.

In order to convert the above dibromo-derivative into the bromohydrin, $MeO{\cdot}C_6H_4{\cdot}CH(OH){\cdot}CH_2Br$, it was dissolved in acetone containing 10 per cent. of its weight of water, and the solution kept at the ordinary temperature (Auwers and Miller, *Ber.*, 1902, **35**, 114). It was ascertained, by titrating at intervals aliquot portions of the mixture, that the reaction proceeded regularly, and was completed quantitatively at the end of about seven and a-half hours. On isolating the bromohydrin, however, this compound was found to be a liquid. Nevertheless, the exact quantitative character of the change left no doubt regarding the nature of the product. With the endeavour to prepare an acetyl derivative from the liquid bromohydrin, the latter was heated with acetyl chloride. This resulted in the formation of a solid, which crystallised from light petroleum in needles, melting at 39—40°, and proved to be *α-chloro-β-bromo*-p-*methoxy*-α-*phenylethane*,

$MeO{\cdot}C_6H_4{\cdot}CHCl{\cdot}CH_2Br$:

0·2223 gave 0·2939 AgBr + AgCl. Br + Cl = 46·0.

$C_9H_{10}OClBr$ requires Br + Cl = 46·3 per cent.

The bromohydrin was treated with ammonia under a great variety of conditions, but only small amounts of basic products

could be obtained, even when anhydrous, liquid ammonia was employed. The chief products were, in every case, resinous materials and volatile, unsaturated oils. Experiments with the use of potassium phthalimide were equally unsuccessful. The small yields of basic products which were obtained from the bromohydrin by means of ammonia were fractionally precipitated as picrate. In this manner it was found that at least two compounds were present, one of which yielded a *picrate*, forming flattened needles, melting at 215°. The *base* from the latter crystallised from benzene in cubes, which melted at 165—166°:

0·0520 gave 0·1394 CO_2 and 0·0348 H_2O. C = 73·1; H = 7·4.
$C_9H_{11}ON$ requires C = 72·5; H = 7·3 per cent.

It would thus appear probable that this compound was the base, $MeO{\cdot}C_6H_4{\cdot}CH{:}CH{\cdot}NH_2$.

The other *picrate* obtained formed stout prisms, melting at 188°, and the corresponding *base* yielded a *benzoyl* derivative crystallising in needles, which fused at 108°, but the amounts were too small for analysis.

m-*Aminostyrene.*

m-Aminostyrene was prepared from *m*-nitrobenzaldehyde by Komppa's method (*loc. cit.*). It was converted into its hydrochloride by passing dry hydrogen chloride into the dry ethereal solution of the base. The salt thus obtained could not be crystallised until water was introduced. The latter was then absorbed, with the evolution of heat, when crystallisation rapidly ensued. The product so obtained was crystallised from alcohol, and then formed well-defined prisms, which melted at 181°:

0·1342, dried at 100°, gave 0·2705 CO_2 and 0·0581 H_2O. C = 55·0; H = 7·0.

0·3506 gave 0·2870 AgCl. Cl = 20·3.

C_8H_9N,HCl,H_2O requires C = 55·3; H = 6·9; Cl = 20·3 per cent.

Although the water present in this hydrochloride was not expelled at 150°, it was, nevertheless, retained as water of crystallisation. This was shown by the fact that the amorphous, anhydrous hydrochloride was again obtained from the regenerated base by treatment with dry hydrogen chloride.

Benzoylaminostyrene, prepared by the Schotten-Baumann method, crystallises from alcohol in hexagonal plates, melting at 126—127°, and, like the foregoing compound, tenaciously retains one molecule of water of crystallisation:

0·1377, dried at 130°, gave 0·3755 CO_2 and 0·0796 H_2O. C = 74·4; H = 6·4.

0·0998, dried at 130°, gave 0·2747 CO_2 and 0·0586 H_2O. C = 75·1; H = 6·5.

$CH_2{:}CH{\cdot}C_6H_4{\cdot}NH{\cdot}CO{\cdot}C_6H_5,H_2O$ requires C = 74·7; H = 6·2 per cent.

Komppa (*loc. cit.*) apparently regarded this compound as being anhydrous, and stated that it melted at 90—91°.

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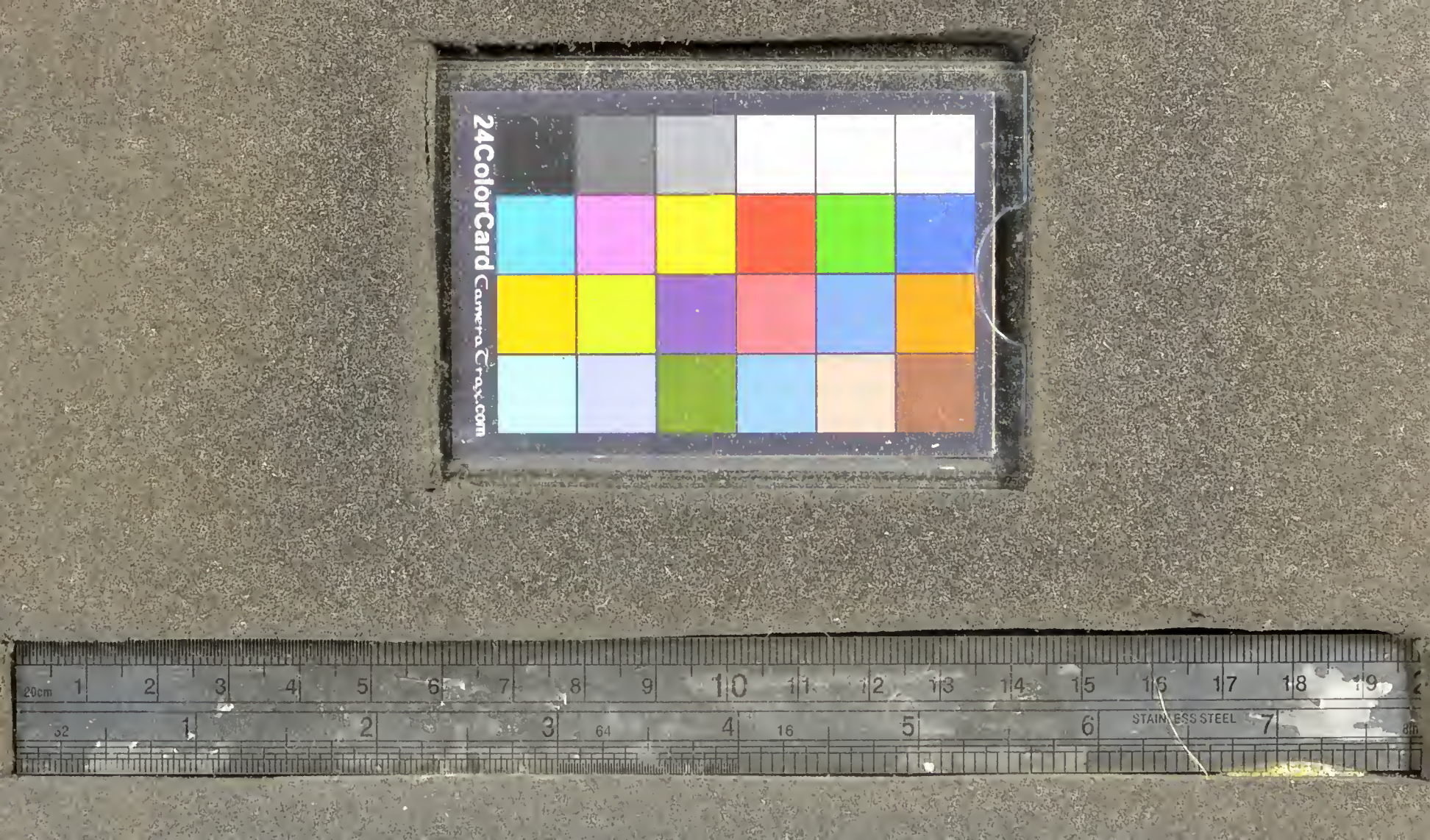
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